Personalized Benefit-Risk Assessment

Maria Costa (Novartis) & Gerd Rosenkranz (Medical University of Vienna)

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Disclaimer

- Maria Costa is an employee of Novartis. The views expressed here are those of the presenter and should not be understood or quoted as being made on behalf of Novartis or institutions to which the presenter is affiliated.
Outline

- Motivation
- Joint modelling of benefit & risk
- Simulation study
- Next steps & discussion
Motivation

A patient consults with her doctor on a specific illness

Doctor needs to predict which intervention has a more favourable benefit-risk for this specific patient: drug A or drug B?
Motivation

A *patient consults* with her *doctor* on a specific illness

Doctor needs to *predict* which *intervention* has a more *favourable benefit-risk* for this *specific patient*: drug A or drug B?

- Neutrophils
- Eosinophils
- Smoking history
- Prior corticosteroid use

*Personalized Benefit-Risk Assessment*

Maria Costa & Gerd Rosenkranz
A patient consults with her doctor on a specific illness. Doctor needs to predict which intervention has a more favourable benefit-risk for this specific patient: drug A or drug B?

- Neutrophils: <1500/mm³
- Eosinophils: >300 cells/µL
- Smoking history: >10 pack years
- Prior corticosteroid use: Yes
Motivation

A patient consults with her doctor on a specific illness.

Doctor needs to predict which intervention has a more favourable benefit-risk for this specific patient: drug A or drug B?

- Neutrophils: <1500/mm³
- Eosinophils: >300 cells/µL
- Smoking history: >10 pack years
- Prior corticosteroid use: Yes

Drug B likely to result in better outcomes overall.
Joint modelling of benefit & risk

- Use generalized linear mixed models (GLMM)
  - Assume \( J \) different outcomes on same subject (each following some distribution)
  - For subject \( i \) with mean response \( \mu_i, g(\mu_i) = X_i b + Z_i u_i, u_i \sim N(0, f(X_i)) \)
Joint modelling of benefit & risk

- Use **generalized linear mixed models** (GLMM)
  - Assume *J different outcomes* on same subject (each following some distribution)
  - For subject *i* with mean response $\mu_i$, $g(\mu_i) = X_i b + Z_i u_i$, $u_i \sim N(0, f(X_i))$

- Random effect $u_i$ is **shared** across all *J* observations for subject *i* thus **modelling potential correlation between efficacy and safety outcomes**
Joint modelling of benefit & risk

- Use **generalized linear mixed models** (GLMM)
  - Assume \( J \) different outcomes on same subject (each following some distribution)
  - For subject \( i \) with mean response \( \mu_i, g(\mu_i) = X_i \beta + Z_i u_i, u_i \sim N(0, f(X_i)) \)

- Random effect \( u_i \) is **shared** across all \( J \) observations for subject \( i \) thus **modelling** potential correlation between efficacy and safety outcomes

- If \( g(\mu_i) \neq \text{identity} \), fixed effects \( \beta \) are **conditional** on random effects \( u_i \)
  - **Monte Carlo integration** can be used to obtain **marginal population effects** – important when making **inferences at the population** level

- **Constraints** may be necessary to ensure **identifiability** for certain distributions
Simulation study
Data generating process

- **Two treatment arms**: new drug vs comparator (1:1 ratio)
- Assume **1 continuous efficacy** and **1 binary safety outcomes per subject** are of interest for BR assessment
- Assume that **2 independent binary covariates**, $X_1$ and $X_2$, have been identified that impact the **performance** of the **new drug**
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- Generate simulated data using the NORTA algorithm and the parameterization

\[
g(\mu_E) = b_{E0} + \sum_{i=1}^{2} X_i b_{Ei} + \left(b'_{E0} + \sum_{i=1}^{2} X_i b'_{Ei}\right) h \\
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Treatment group indicator: $h = 1$ if new drug, 0 otherwise
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Interaction effect between new drug and covariate $X_i$
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Mean effect of new drug when $X_1 = X_2 = 0$
Simulation study
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Mean effect of comparator arm
Simulation study
Modelling approach

- GLMM approach to model jointly efficacy and safety data
- Both frequentist estimation and Bayesian inference used to assess ability to identify subset of covariate space corresponding to “positive” BR profile
  - For Bayesian inference non-informative priors used throughout
  - Bayesian approach can be particularly useful in the context of BR – represent uncertainty through probability statements, prediction of BR profile, etc
Simulation study
Assumptions and parameter values

- Continuous **efficacy outcome** (e.g., primary efficacy endpoint): $N(\mu, \sigma^2)$
- Binary **safety outcome** (e.g., AESI): Bernoulli ($p$), with logit link function
- Set **correlation** between efficacy and safety outcome to **0.5 for new drug, 0 for comparator arm**

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- Probability of covariates $X_1$ or $X_2$ being present is 0.3–49% with $X_1 = X_2 = 0$, 21% with $X_1 = 1$ and $X_2 = 0$ or vice-versa, and 9% with $X_1 = X_2 = 1$
- Sample size = 200 / arm
- 1000 simulated datasets generated and analysed for each scenario
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- Set correlation between efficacy and safety outcome to **0.5 for new drug, 0 for comparator arm**
- Set $b_{EI} = b_{Si} = 0$, since these parameters do not play a role in assessing treatment effect
- Set $b_{E0} = 0$, corresponding to no **efficacy effect in comparator arm**
- Set $b_{S0} = 0$, corresponding to **safety event probability of 0.5 in comparator arm**
- Probability of covariates $X_1$ or $X_2$ being present is 0.3
  - 49% with $X_1 = X_2 = 0$, 21% with $X_1 = 1$ and $X_2 = 0$ or vice-versa, and 9% with $X_1 = X_2 = 1$
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Simulation study
Benefit-risk profiles

- Treatment effect of the new drug, $h = 1$, over the comparator, $h = 0$, is given by
  - Efficacy: $D_E(X) = b'_E0 + \sum_{i=1}^{2} X_i b'_{Ei}$
  - Safety: $D_S(X) = b'_S0 + \sum_{i=1}^{2} X_i b'_{Si}$

- Benefit-risk profiles take the form
  - $D_E(X) < e$
  - $\exp(D_S(X)) = OR(X) < s$
Simulation study
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- Benefit-risk profiles take the form
  - $D_E(X) < e$
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Simulation study

Probability that new drug satisfies BR profile $D_E(X) < -0.2$ and $\text{OR}(X) < 0.9$

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**Low probability of positive BR in the absence of no overall improvements in efficacy and safety**
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Low probability of positive BR across subgroups if overall increase in safety signal.
## Simulation study

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Probability of positive BR in different subgroups adapts to assumptions on behavior of new drug within each subgroup.
# Simulation study

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Subgroup size has some impact on probability of positive BR
Next steps...

- Incorrectly assigning treatment to a subgroup of patients may have different consequences in terms of benefit or risk:
  - Not treating a subgroup whose patients respond better than in the compliment risks treating patients with an inefficacious treatment
  - Treating a subgroup where the intervention causes severe side effects puts this subgroup under unnecessary risk – all efforts should be made to avoid this scenario

- These different trade-offs could be represented in terms of utility functions to convey the difference in penalty to pay for the different decisions
Discussion

- Desirable to optimise treatment assignment to subgroup of patients that benefit the most from both an efficacy and safety perspective

- Still early stages...
  - Using joint models for both efficacy and safety allows allocation of patients to treatment taking into account these two dimensions and their potential correlation
  - But need to further explore this approach: sample size, signal-to-noise ratio, correlation, etc

- Benefit-risk decisions are complex by definition
  - Can utility functions add clarity to implicit trade-offs when modelling these data?
  - How to incorporate preference/weighting information into the model?
References


- Gerd Rosenkranz, *Can we identify patients at high risk of harm under a generally safe intervention?* European Statistical Meeting on Analysis of Safety Data in Clinical Trials. Leiden, June 23rd 2017

Thank you!

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Simulation study – part 2

Non-inferiority trials

- In a non-inferiority trial, BR profiles of interest may extend to scenarios where efficacy and safety are similar across treatment groups.
## Simulation study – part 2
### Probability that new drug satisfies non-inferiority BR profile

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<th>$X_1 = 1, X_2 = 0$ (21%)</th>
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<th>$X_1 = X_2 = 1$ (9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$D_E(X)$</td>
<td>OR($X$)</td>
<td>P(+/ve BR)</td>
<td>$D_E(X)$</td>
</tr>
<tr>
<td>No treatment effect</td>
<td>0</td>
<td>1</td>
<td>33%</td>
<td>0</td>
</tr>
<tr>
<td>Overall better efficacy &amp; no safety signal</td>
<td>-0.5</td>
<td>1</td>
<td>53%</td>
<td>-0.5</td>
</tr>
<tr>
<td>Better efficacy if $X_1 = 1$ &amp; no safety signal</td>
<td>0</td>
<td>1</td>
<td>33%</td>
<td>-0.5</td>
</tr>
<tr>
<td>Overall better efficacy &amp; worse safety</td>
<td>-0.5</td>
<td>1.3</td>
<td>18%</td>
<td>-0.5</td>
</tr>
<tr>
<td>Overall better efficacy &amp; worse safety if $X_1 = 1$</td>
<td>-0.5</td>
<td>1</td>
<td>55%</td>
<td>-0.5</td>
</tr>
<tr>
<td>Better efficacy if $X_1 = 1$ &amp; worse safety if $X_2 = 1$</td>
<td>0</td>
<td>1</td>
<td>33%</td>
<td>-0.5</td>
</tr>
<tr>
<td>No overall efficacy &amp; Better safety if $X_1 = 1$</td>
<td>0</td>
<td>1</td>
<td>33%</td>
<td>0</td>
</tr>
</tbody>
</table>